We Claims

1. A method for cloning genes of a biosynthetic pathway, comprising
   i) providing host cells containing a replicable vector including genomic DNA isolated from a source of uncultivated microrganisms, which host cells are provided under conditions wherein expression of open reading frame sequence(s) of the genomic DNA occurs; and
   ii) detecting the presence or absence of a biosynthetic pathway which is dependent on expression of at least one of the opening reading frames by the host cells.

2. A method for identifying a compound produced by a biosynthetic pathway, comprising
   i) providing host cells containing a replicable vector including genomic DNA isolated from a source of uncultivated microrganisms, which host cells are provided under conditions wherein expression of open reading frame sequence(s) of the genomic DNA occurs; and
   ii) detecting compound produced by the host cells.

3. The method of claim 1 or 2, wherein the biosynthetic pathway produces or transmutes a non-polymeric compound.

4. The method of claim 1 or 2, wherein the biosynthetic pathway produces or transmutes a non-proteinaceous compound.

5. The method of claim 1 or 2, wherein the biosynthetic pathway produces a compound having a molecular weight less than 7500amu.

6. The method of any of claims 2-5, wherein the compound is a direct product of endogenous precursors for the biosynthetic pathway.

7. The method of any of claims 2-5, wherein the compound is synthesized *de novo*.

8. The method of any of claims 1 or 2, wherein the vector includes at least 20 kilobases of genomic DNA.

9. The method of claim 8, wherein the vector includes at least 50 kilobases of genomic DNA.

10. The method of claim 1 or 2, wherein the source of uncultivated microrganisms includes prokaryotic cells.

11. The method of claim 10, wherein the source of uncultivated microrganisms includes prokaryotic cells of the Archaea Domain.

12. The method of claim 11, wherein the source of uncultivated microrganisms includes Archaea cells selected from the group consisting Crenarachaeota, Euryarachaeota, Karachaeota, and combinations thereof.

13. The method of claim 1 or 2, wherein the uncultivated microrganisms are isolated from soil samples, insect intestines, plant rhizospheres, microbial mats, sulfur pools samples, or marine samples.

14. The method of claim 1 or 2, wherein the source of uncultivated microrganisms includes prokaryotes having low low G/C content genomes.

15. The method of claim 1 or 2, wherein the source of uncultivated microrganisms includes anerobes.

16. The method of claim 1 or 2, wherein the host cells comprise a variegated population of vectors containing different genomic DNA sequences.

17. The method of claim 16, wherein genomic DNA has an average length of at least 20 kilobases in length.

18. The method of claim 16, wherein variegated population of vectors include genomic DNA from at least 10 different microorganism species.

19. The method of claim 1 or 2, wherein the host cells are a species of Bacteria selected from the group consisting of Acetobacter, Actinomyces, Aerobacter, Agribacterium, Azotobacter, Bacillus, Bacteroides, Bordetella, Brucella, Chlamydia, Clostridium, Corynebacterium, Erysipelothrix, Escherichia, Francisella, Fusobacterium, Haemophilus, Klebsiella, Lactobacillus, Listeria, Mycobacterium, Myxococcus, Neisseria, Nocardia, Pasteurella, Proteus, Pseudomonas, Rhizobium, Rickettsia, Salmonella, Serratia, Shigella, Spirilla, Spirillum, Staphylococcus, Streptococcus, Streptomyces, Trepanema, Vibrio, Vibrio, and Yersinia.

20. The method of claim 19, wherein the host cells are a species of Escherichia or Streptomyces.

21. The method of claim 20, wherein the host cells are Escherichia coli.

22. The method of claim 1 or 2, wherein the vector is a low-copy number vector.

23. The method of claim 22, wherein the vector is a single-copy number vector.

24. The method of claim 22, wherein the vector is a BAC or PAC vector.

25. The method of claim 2, wherein production of the compound is detected by an ability to induces a biological or biochemical response from a test cell.

26. The method of claim 2, wherein the response from test cell comprises: a phenotypic change, a change in gene transcriptional rates, a change in phosphorylation states, a change in 2nd messenger formation, cell quiescence, cell death.

27. The method of claim 2, wherein production of the compound is detected by spectrometric detection.

28. The method of claim 2, wherein production of the compound is detected by chromatographic detection.

29. The method of claim 2, wherein production of the compound is detected in a cell-free assay.

30. The method of claim 2, wherein production of the compound is detected by an ability to induces a biological or biochemical response from the host cell.

31. The method of claim 1, comprising the further step of identifying or isolating individual genes from the genomic DNA which produce biosynthetic pathway.

32. The method of claim 2, comprising a further step of identifying the chemical structure of compound.

33. The method of claim 2, comprising a further step of formulating a pharmaceutical composition including one or more compounds produced by the host cell.

34. A cell engineered with a replicable vector including heterologous genomic DNA isolated from a source of uncultivated microrganisms, which host cell produces a compound in a manner dependent on expression of at least one opening reading frame of the genomic DNA.

35. A library of cells comprising a replicable vector including heterologous genomic DNA isolated from a source of uncultivated microrganisms, wherein the library includes a variegated population of genomic DNA sequences, and at least a portion of the cells produce a compound in a manner dependent on expression of at least one opening reading frame of the genomic DNA.

36. An isolated nucleic acid comprising one or more genes from a source of uncultivated microrganisms, wherein expression of the genes in a heterologous host cell provides a functional biosynthetic pathway for production of a compound in a manner dependent on expression of the genes.

37. A purified form of a compound which can be produced by the cell of claim 34.

38. A pharamaceutical preparation of a compound which can be produced by the cell of claim 34.

39. A library of compounds produced by the cells of claim 35.

40. A method for cloning genes of a biosynthetic pathway, comprising
    i) cloning, into a replicable vector, genomic DNA isolated from a source of uncultivated microrganisms;
    ii) expressing open reading frame sequence(s) of the genomic DNA in host microorganisms that harboring the vector; and
    iii) detecting the presence or absence of a biosynthetic pathway which is dependent on expression of at least one of the opening reading frames by the host microorganisms.

41. A method for identifying a product of a biosynthetic pathway, comprising
    i) cloning, into a replicable vector, genomic DNA isolated from a source of uncultivated microrganisms;
    ii) expressing open reading frame sequence(s) of the genomic DNA in host microorganisms harboring the vector; and
    iii) detecting a compound which is the product of a biosynthetic pathway that is dependent on expression of at least one of the opening reading frames by the host microorganisms.

42. A method for identifying a small molecule produced by a microorganism, comprising
    i) providing one or more host cells, a plurality of which each contain a replicable vector including genomic DNA isolated from a source of uncultivated microrganisms,
    ii) maintaining the host cells under conditions permitting gene expression; and
    iii) detecting the presence of a small molecule produced by one or more of the host cells transfected with the genomic DNA.

43. A method for identifying a genetically engineered host cell which produces a small molecule of interest, comprising
    i) providing one or more host cells, a plurality of which each contain a replicable vector including genomic DNA isolated from a source of uncultivated microrganisms,
    ii) maintaining the host cells under conditions permitting gene expression;
    iii) detecting the presence of a small molecule produced by one or more of the host cells transfected with the genomic DNA; and

iv) identifying the host cell which produces the small molecule.

44. A method for producing a small molecule of interest, comprising

i) providing a host cell which contains genomic DNA originally isolated from a source of uncultivated microrganisms; and

ii) maintaining the host cell in a culture medium and under conditions permitting the production of the small molecule.

45. A method of claim 2C which further comprises separately recovering the small molecule from the host cells and medium.